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Discussion (Research Issues to Facilitate Risk Assessment of Toxic Air Pollutants)

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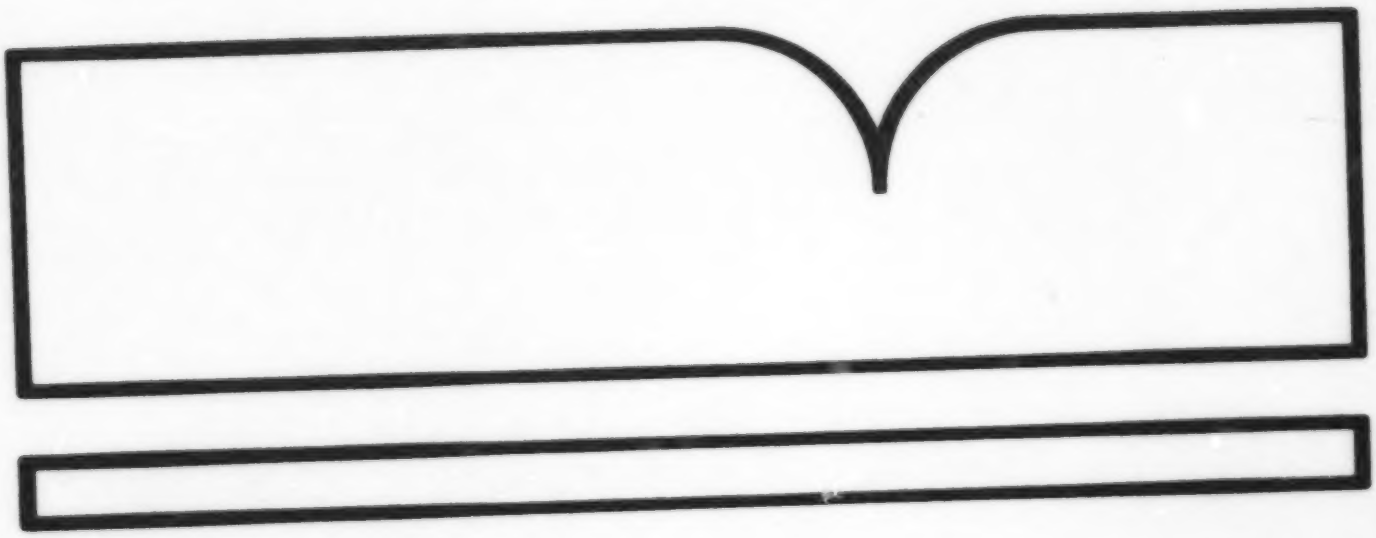

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16. ABSTRACT

Given the excellence of the "Critical Review of Toxic Air Pollutants", my discussion will expand on a few points raised by Dr. Goldstein rather than critique his comments. Because Dr. Goldstein and the other discussants have addressed carcinogenesis issues so well, I will limit my comments to non-carcinogenic endpoints. My focus will be on health research elements which feed into risk assessment using the basic premise that a risk assessment can be no better than the data being assessed. The discussion will be organized according to the elements of research risk assessment and risk management described by Dr. Goldstein and the National Academy of Sciences panel. Dr. Goldstein's convention of TAP, standing for Toxic Air Pollutants, will be used.

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Discussion

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JOURNAL ARTICLE

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Given the excellence of the Critical Review of toxic air pollutants, my discussion will expand on a few points raised by Dr. Goldstein rather than critique his comments. Because Dr. Goldstein and the other discussants have addressed carcinogenesis issues so well, I will limit my comments to noncarcinogenic endpoints. My focus will be on health research elements which feed into risk assessment using the basic premise that a risk assessment can be no better than the data being assessed. The discussion will be organized according to the elements of research risk assessment and risk management (Figure 1) described by Dr. Goldstein and the National Academy of Sciences panel.[1] Dr. Goldstein's convention of TAP, standing for Toxic Air Pollutants, will be used.

Laboratory and Field Observations of Adverse Health Effects

Laboratory and field data permit hazard identification which, by establishing whether a given chemical(s) causes an adverse effect, is the first step in risk assessment. It is also one of the most difficult goals to achieve since far more is required than performing a multitude of scientifically sound studies. Inherent problems and a few of the potential solutions are discussed below.

Critical Review Discussion

Development of an Adequate Health Data Base

As Dr. Goldstein notes, there are thousands of TAP, but only a few have health data bases which permit a sophisticated hazard identification. It is also likely that the national resources are not available to adequately study the toxicity of every chemical emitted into the atmosphere using current methodologies. This basic problem has been recognized for some time, causing genotoxicologists to develop tier testing approaches for mutagenesis and carcinogenesis. Others in immunotoxicology, neurotoxicity, and reproductive toxicity are equally cognizant of the problem, but their development of tier testing approaches is not yet as advanced. Similar programs in pulmonary toxicology have not seriously begun. Years will be required before all these testing programs are validated and available. Thus, an interim approach will be required to ensure that research resources are applied coherently in a targeted fashion to best improve the data base.

Development of such a targeted health research program is confounded by a paucity of monitoring data and the large numbers of chemicals of interest. One of the potential solutions would be to perform "mini-assessments" which would be used solely to provide research guidance. At present, relatively sophisticated assessment documents are being prepared by EPA and other governmental organizations. Because these documents form the foundation for regulatory decision making, they are typically expensive and require lengthy periods of writing and review before completion. This restricts the number of such documents available. Fortunately, the National Library of Medicine is seeking to compress data bases to permit an overview of a large number of chemicals. A good example is the Toxicology Data Base which incorporates the Gene-Tox and several other data bases. As of July 1983, records for 4021 compounds are available and about 6500 chemicals will be in the data bank by 1986. At present there are 907 skeleton records having minimal toxicity data which are now being reviewed for updating. The data base contains information on chemical structure, physical properties, toxicity, and metabolism, in addition to other hazardous properties. Chemicals are selected for review or periodic updating by the Peer Review Committee of expert toxicologists which meets four times per year. The Committee incorporates the primary literature for the chosen chemicals. Information is also drawn from other computerized literature files such as Chemical Abstracts, TOXLINE, TOXBACK, and MEDLINE. The Toxicology Data Bank is computerized and on-line through the National Library of Medicine telephone network.

To make research decisions for initiating a TAP program a mini-assessment using this data bank might be helpful. The prefix, mini, does not refer solely to length, since even a full risk assessment document will be short if few data are available. Rather, it refers to a short overview of the health effects and monitoring data for a large number of chemicals. It would be long on tables and references, but short in text, enabling it to be completed rapidly and inexpensively. When a series of these became available, a committee of experts from several disciplines (genotoxicity, immunotoxicity, neurotoxicity, pulmonary toxicity, liver/kidney toxicity, and developmental toxicity) could review the mini-assessments for the purpose of recommending research of greatest relevance. This would enable us to go beyond the realm of an individual scientist proposing research of interest to him, which, although it would increase the toxicology data base, would not necessarily address the most critical issues in toxicology which must be addressed for optimal protection of the public health.

Improved Utilization of the Currently Available Data Base

For several TAP, many studies are available. However, they may be from oral exposures, when inhalation or dermal exposure is the natural route. They may also be on a species of

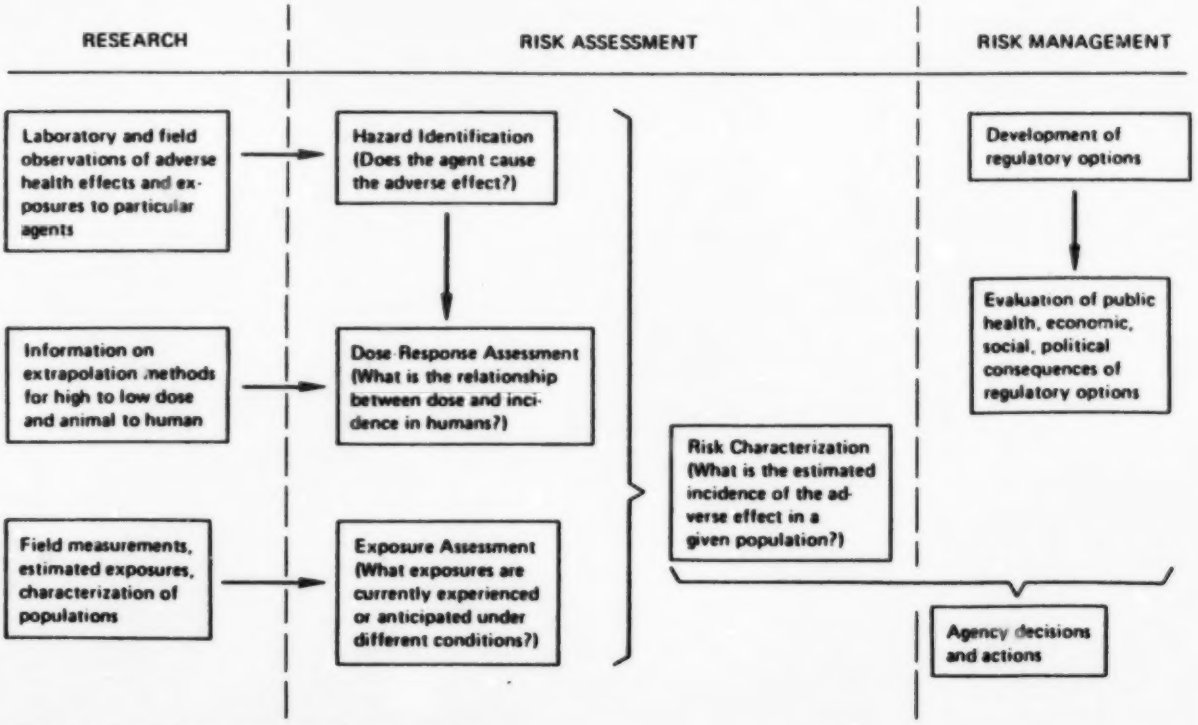
RESEARCH
RISK ASSESSMENT
RISK MANAGEMENT
Laboratory and field observations of adverse health effects and exposures to particular agents
Hazard Identification (Does the agent cause the adverse effect?)
Development of regulatory options
Information on extrapolation methods for high to low dose and animal to human
Dose-Response Assessment (What is the relationship between dose and incidence in humans?)
Evaluation of public health, economic, social, political consequences of regulatory options
Risk Characterization (What is the estimated incidence of the adverse effect in a given population?)
Field measurements, estimated exposures, characterization of populations
Exposure Assessment (What exposures are currently experienced or anticipated under different conditions?)
Agency decisions and actions

Figure 1. Elements of risk assessment and risk management.

the chemical which is atypical in the air (e.g., a metal chloride instead of a metal oxide). When a chemical is of interest because of its existing data base, but that existing data base has weaknesses such as those described above, a few studies designed to compare the "real world" situation to the previous "experimental" situation might prove helpful. Principles derived from such comparisons could be applied to the existing data base to facilitate interpretation.

Adverse Effects

"Adverse effects" is a recurring phrase in risk assessment since protecting the public from adverse effects is the ultimate goal of assessments and regulations. However, aside from very severe effects like mortality, there is no scientific concensus on the definition of an adverse health effect. Frequently, research utilizing near-ambient exposures indicates that a chemical causes a statistically significant change in a parameter without providing information on the biological significance of that change. For example, suppose there is a statistically significant 20% decrease in the ability of lypopolysaccharide-stimulated lymphocytes to incorporate ^{3}H-thymidine. Does this mean that the subject will be unable to defend himself against infectious disease? The list could go on and on. One way to improve the interpretability of such studies is via research on mechanisms. If researchers can determine why a change occurs and the placement of that change within a continuum of effects leading to overt clinical disease, then policy makers can better relate a given change to disease outcome and make judgments on the adversity of the change.

Research Descriptions

In making judgments on hazards, the policy maker turns to the data base. If a study is described poorly by the researcher, others have great difficulty in using it for decision making. Since researchers work toward the goal of public health, they should be aware that occasionally they inhibit their own aims. As a case in point, there is a recent elegant animal toxicology study on health effects of ozone. However, for a few effects, it is impossible for the reader to determine what concentrations caused the effects. For their work to have maximal impact, researchers should be aware of the need for precise descriptions, particularly of methods (typically, weaknesses are found in exposure and statistical descriptions).

Extrapolation Methods

The second element is extrapolation from animal to man and from high to low dose for use in dose-response assessment. Since the largest and often the most descriptive portion of the data base will be from animal studies, extrapolations are imperative. The issue, then, is to improve the scientific approaches for extrapolation.

High to Low Dose Extrapolation

This type of extrapolation is discussed by Dr. Goldstein and other discussants, primarily from a carcinogenic viewpoint, and therefore will not be expanded. Rather, the focus here will be on non-carcinogenic effects. Typically, when investigators attempt to extrapolate from high to low dose, they rely on Haber's rule, which states that the product of concentration (C) and time of exposure (T) results in a given level of toxicity. If this were true, then a mouse exposed to a $C \times T$ of 7 would exhibit a given magnitude of effect whether it were exposed to 1 ppm for 7 h or 7 ppm for 1 h. Although convenient, this rule is not universally true.[2,3] As Dr. Goldstein stated, dose-rate appears to be the controlling factor. For studies of pollutant interactions, simplistic views of high to low dose extrapolation can be particularly confounding. Consider an experiment in which an animal is exposed to high levels of a gas and a particle. The high level of gas might alter pulmonary function and clearance, altering the site of deposition and the retention of the particle, thereby permitting the particle to express a toxicity which would not have occurred if the concentration of gas were lower and without significant effect.

There are no easy definitions of "high" and "low" levels of pollutants, particularly considering the unknown animal to man extrapolation. However, we as animal researchers must be cognizant of inherent problems in high dose studies, such as the potential for initiating mechanisms of toxicity which would not occur in man at ambient levels. There also needs to be a broader perspective across disciplines. For example, just because "low" levels of a chemical have no effect on the immune system, it does not necessarily mean that "low" levels are not toxic to other systems. This sounds obvious, but such assumptions abound. Consider the number of chemicals called kidney (or other organ) toxins which have never been examined for pulmonary effects. Too often the lack of data is translated into negative data.

Animal to Man Extrapolation

Since this type of extrapolation for air pollutants not having toxic metabolites has been discussed elsewhere[4] and is the subject of a recent workshop,[5] it will be dealt with briefly here. Extrapolation has two basic components: qualitative and quantitative. Qualitative extrapolation refers to the issue of whether a chemically-induced effect in animals will also occur in man. It is the general basis of animal toxicology that if an effect occurs in a number of animal species, it is likely that this effect will occur in man. The basic premise is that the ultimate mechanism of toxicity is interaction of the chemical (or its metabolites/toxic products) with molecules of the subjects. Because of the shared molecules in all higher animal species (including man), qualitative extrapolations are made. Because of species differences in metabolism and other species differences, the phrase "in a number of animal species" is included. Although qualitative extrapolation is generally accepted, there are specific issues which require targeted research.

Quantitative extrapolation is the next step—if the qualitative extrapolation holds, at what concentration will man experience the effect? Quantitative extrapolation can be divided into two issues: dosimetry and sensitivity. Dosimetry refers to the dose to the target tissue and thus is a reflection of deposition and clearance. Species sensitivity refers to the response of different animal species to the same tissue dose. For example, even if mouse and man receive an equivalent dose to the respiratory bronchiole, differences in defense/repair mechanisms may result in a differing sensitivity.

A quantitative animal to man extrapolation is more reasonably achievable for TAP not having toxic metabolites. However, with more intense research programs on toxicokinetics of inhaled TAP, hopefully the level of difficulty for extrapolating TAP with toxic metabolites will decrease in the future.

Field Measurements, Estimated Exposures, Characterization of Populations

This last element provides information for exposure assessment, and a portion of it can be advanced by biomedical research.

Dosimetry research (described above) with humans can be of significant benefit to this element. For example, there is a reasonable data base on the deposition of insoluble particles (up to about 10 μm, aerodynamic diameter) in the lungs of healthy adult males.[6] This data base on particles is being ex-

panded by several laboratories, including ours, to include hygroscopic particles, larger particles, deposition in the lungs of children, persons with preexisting disease, and exercising individuals. When completed, these data can be interrelated with field measurements of particles (concentrations, physiochemical data) and demographic data (numbers and types of individuals and potential exposure lengths) to determine what dose would be deposited in the lungs of the populace of interest. This example was chosen since it is the closest to fruition. Gases and hygroscopic particles are more difficult because their physiochemical properties play a far greater role in deposition than those properties for insoluble particles. Thus, more direct experimentation in animals and humans would be required on a per chemical basis.

Characterization of populations is also in this element, but it needs to extend beyond the determination of dose received. The impact of the dose needs to be considered, vis-a-vis potentially susceptible populations. This subject is inherent in the above discussions as well. Differential susceptibilites have been established for some population groups and for some pollutants. For example, asthmatics are more sensitive to sulfur dioxide.[9] In other situations, the relationship of a potentially different dose to sensitivity has not been established. Even within an apparently "normal" population, responsivity to ozone differs.[5] Considering the large number of TAP and the health data base, very little is known about potentially susceptible subpopulations. However, by being alert to the issue, carefully targeted studies can be performed, as warranted.

Summary

In the foregoing, I have raised several problems that must be addressed if research is to be of greater benefit to risk assessment for TAP. Neither the problems nor selected proposed solutions are intended to be complete. Rather, they are designed to stimulate discussion among researchers who share the goal of providing data to benefit the public health. We must understand that our goal does not exist in a vacuum, but that it is shared alike by individuals in risk assessment and the policy makers in risk management. Achievement of the goal will be facilitated by increased communication between these three groups. Synergism can be more than a toxicological manifestation of interaction.

Disclaimer

This report has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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